UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/822,186	03/20/97	RUEGER D	CRP-137

18N2/0109

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EXAMINER	
ROMEO, D	

ART UNIT	PAPER NUMBER
1812	

DATE MAILED: 01/09/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/822,186	Rueger et al.
Examiner: David Romeo 11/4/98	Group Art Unit: 1812

☒ Responsive to communication(s) filed on *Jun 20, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-34* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-34* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-34 are pending and are being examined.

Claim Objections

2. Claim 2 is objected to because of the following informalities: "BMP9" is misspelled. Appropriate correction is required.

3. Claim 18 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Approximately at least 2.5 mg of OP-1 fails to further limit approximately 1.25 mg of OP-1.

Claim Rejections - 35 USC § 112

4. Claims 2-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a device comprising an osteogenic protein wherein said osteogenic protein is selected from the specifically recited osteogenic proteins, or wherein said osteogenic protein comprises an amino acid sequence having at least 70% homology with the C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of human OP-1 and induces local bone and or cartilage formation, does not reasonably provide enablement for a

device comprising an osteogenic protein wherein said osteogenic protein is an amino acid sequence variant of the specifically recited osteogenic proteins or wherein said osteogenic protein comprises an amino acid sequence having at least 70% homology with the C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of human OP-1 without regard to the functional activity of the osteogenic protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Amino acid sequence variants of the recited osteogenic proteins encompasses conservative and non-conservative amino acid substitutions, insertions and deletions, which may or may not affect the functional activity of the protein, and the specification has not taught which amino acid residues are tolerant and which are intolerant of substitution, deletion or insertion such that the skilled artisan could obtain an amino acid sequence variant without undue experimentation. The specification does not exemplify additional amino acid sequence variants of the recited osteogenic proteins and it is unpredictable what level of amino acid sequence can be tolerated while retaining functional activity. The skilled artisan is left to perform extensive trial and error experimentation wherein amino acid substitutions, insertions and deletions are made in the recited osteogenic proteins until a functional osteogenic protein is obtained. Such trial and error experimentation is considered undue. Furthermore, the specification has not taught how to use a non-functional osteogenic protein. Given the limited guidance and working examples in the specification, the unpredictability in the art, and the extensive amount of experimentation required of the skilled artisan to obtain amino acid sequence

variants, undue experimentation would be required to practice the full scope of the claimed invention.

5. Claims 26-30, 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26-28 are indefinite over the recitation of "defect site" because it is not clear if the method is to be used for any imaginable defect site, bone related or not, or if the method is to be used for bone defect sites. The metes and bounds of the claim are not clearly set forth.

Claims 26-30 are indefinite because the claims lack a process step which clearly relates back to the preamble and it is unclear what effect is to be achieved by the claimed method; an intended use is not the same as an effect; in the absence of a recitation as to any effect, or a process step producing an effect, or an effective amount of the agent to cause an effect, it is unclear what effect can be inferred.

Claim 34 is indefinite because it is not clear how two receptacles comprise a single receptacle. The metes and bounds of the claim are not clearly set forth.

[redacted]

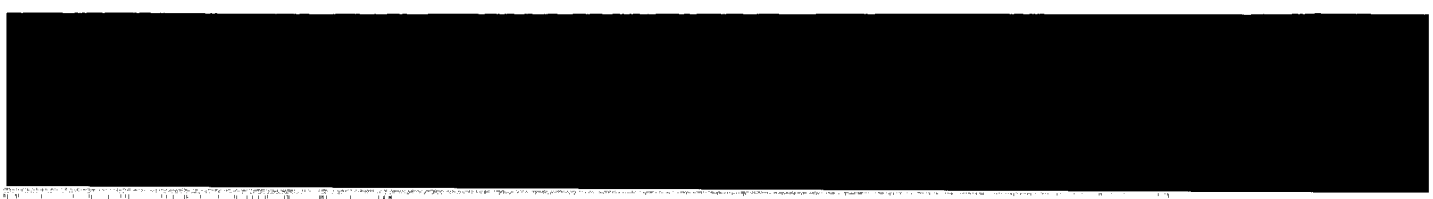
Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 7-15, 20-22, 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Amman et al. (A). Amman et al. disclose a composition comprising an osteogenic protein, wherein said osteogenic protein is TGF-β, a matrix, wherein the matrix is tricalcium phosphate or collagen, and a binding agent, wherein the binding agent is dextran, or carboxymethyl cellulose. Amman et al. also teach said composition comprising an osteogenic protein, wherein said osteogenic protein is TGF-β, and combinations of said matrices and said binding agents (paragraph bridging columns 9-10), said composition further comprising a wetting agent (column 16, full paragraph 5). Amman et al. teach the composition can be used to induce bone at a site where there is a bone deficiency (column 10, full paragraphs 2-3; column 12, full paragraphs 1-2). Amman et al teach said composition wherein the ratio of binding agent to matrix varies from 0.1:1 to 1:1 (Abstract).

8. Claims 1-4, 7-15 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Leary (C). O'Leary et al. teach a composition for use in bone repair, said composition comprising



demineralized bone powder, BMPs, one or more binding agents, and a wetting agent (column 1, line 65 to column 4, line 59).

9. Claims 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Lindstrom et al. (B). Lindstrom et al. disclose a composition comprising an osteogenic protein, i.e. TGF-β (column 1, full paragraph 6), 0.01%-10% binding agent, i.e. hydroxypropylmethylcellulose (column 4, full paragraph 3), and 0.1 ng/ml to 1 g/ml matrix, i.e. collagen (column 6, lines 26-35).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Leary et al. (C) as applied to claim 1 above, and further in view of Ogawa et al. (U). O'Leary et al. teach composition for use in bone repair said composition comprising a BMP, as discussed above. O'Leary et al. do not teach said composition comprising at least two different osteogenic proteins. Ogawa et al. teach that TGF-β and BMP synergize in promoting the formation of endochondral

bone *in vivo* (page 14233, paragraph bridging columns 1-2). Ogawa et al. do not teach the composition of O'Leary et al. comprising TGF-β and BMP. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a composition comprising a BMP, as taught by O'Leary et al., and to modify that teaching by including two different osteogenic proteins, such as TGF-β and BMP, as taught by Ogawa et al., with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to achieve the synergistic effect of two different osteogenic proteins and induce more bone growth. The invention is prima facie obvious over the prior art.

12. Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amman et al. (A) in view of LeGeros et al. (CS, cited by Applicants). Amman et al. disclose a composition comprising an osteogenic protein, a matrix and a binder, as discussed above. Amman et al do not teach said composition comprising a matrix wherein said matrix comprises a combination of HA and TCP. LeGeros et al. teach a matrix comprising a combination of hydroxylapatite (HA) and tricalcium phospahte (TCP) for the repair of periodontal defects and in some orthopedic applications and the combination is more efficient than HA alone. LeGeros et al. do not teach said composition comprising an osteogenic protein and a binding agent. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a composition comprising an osteogenic protein, a matrix and a binder, as taught by Amman et al., and to modify that teaching by using a combination of HA and TCP, as taught by LeGeros et al.,

with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to derive the more efficient biological performance of the HA/TCP combination, as taught by LeGeros. The invention is prima facie obvious over the prior art. .

13. Claims 1, 20-22, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amman et al. (A). Amman et al. disclose a composition comprising an osteogenic protein, a matrix and a binder for inducing bone, as discussed above. Amman et al. also discloses that the TGF-β and TCP are mixed before exposure to the polymer used to bind the mixture. Amman et al. do not disclose a kit for inducing bone formation. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a kit comprising a receptacle containing the TGF-β/TCP mixture and a receptacle containing the binding agent, and to further include a receptacle containing a wetting agent, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make such a kit in order to either sell the kit or to make it available to other investigators. The invention is prima facie obvious over the prior art.

14. Claims 23, 24 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindstrom et al. (B). Lindstrom et al. disclose a composition comprising an osteogenic protein, i.e. TGF-β (column 1, full paragraph 6), 0.01%-10% binding agent, i.e.

hydroxypropylmethylcellulose (column 4, full paragraph 3), and 0.1 ng/ml to 1 g/ml matrix, i.e. collagen (column 6, lines 26-35). Lindstrom et al. also teach that the composition is useful in orthopedic applications. Lindstrom et al. do not teach said composition for the repair of bone. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use the composition, as taught by Lindstrom et al., for the repair of bone, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because TGF-β is an osteoinductive factor. The invention is prima facie obvious over the prior art.

15. Claims 1, 5, 17-19 and 26-31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al. (CD, cited by Applicants) in view of O'Leary et al. (C). Cook et al. teach the induction of bone formation with a composition comprising OP-1 and collagen (page 302, paragraph bridging columns 1-2). The collagen was prepared from demineralized bone (page 303, column 2, full paragraph 1). The composition comprised 500 mg of collagen matrix and 0.625 to 2.5 mg of OP-1 (page 303, column 2, full paragraph 1), which is equivalent to 1000 mg of collagen matrix and 1.25 to 5.0 mg of OP-1. Cook et al. teach the experimental bone defect was filled completely with the composition (paragraph bridging pages 303-304). Cook et al. do not teach said composition comprising carboxymethylcellulose. O'Leary et al. teach composition for use in bone repair, said composition comprising demineralized bone powder (paragraph bridging columns 1-2), which comprises collagen, as taught by Cook et al., BMPs

(paragraph bridging columns 2-3), and carboxymethylcellulose (paragraph bridging columns 3-4). O'Leary et al. also teach that carboxymethylcellulose significantly improves the ability of the composition to keep the bone powder in suspension and makes the application of a homogeneous composition easier. O'Leary et al. teach said compositions wherein the bone powder comprises about 80% by weight of the composition (column 4, full paragraph 1). Thus, the composition taught by O'Leary et al., which comprises carboxymethylcellulose, would comprise about 20% carboxymethylcellulose, which encompasses applicants claimed device comprising approximately at least about 180 or 200 mg carboxymethylcellulose. O'Leary et al. do not specifically teach said composition comprising OP-1. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a composition for inducing bone, as taught by Cook et al., and to modify that teaching by adding carboxymethylcellulose to the composition, as taught by O'Leary et al., with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to improve the suspension-keeping characteristics of the composition. The invention is prima facie obvious over the prior art.

16. Claims 1, 15-19 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al. (CD, cited by Applicants) in view of O'Leary et al. (C). as applied to claims 1, 17-19 above, and further in view of Kuberasampath et al. (AE, cited by Applicants). Cook et al. in view of O'Leary et al. teach a composition comprising OP-1, collagen matrix, and carboxymethylcellulose, as discussed above. Cook et al. in view of O'Leary et al. do not teach

said composition further comprising saline. Kuberasampath et al. teach OP preparations in physiological saline mixed with collagen matrix (column 12, lines 43-46). Kuberasampath et al. do not teach OP preparations in physiological saline mixed with collagen matrix and carboxymethylcellulose. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a composition as taught by Cook et al. in view of O'Leary et al., and to modify that teaching by including saline, as taught by Kuberasampath et al., with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to dissolve the OP-1 in a suitable buffer. The invention is prima facie obvious over the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**stephen.walsh@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH C. KEMMERER
PATENT EXAMINER

DSR
January 4, 1998

[redacted]